Clinical trial results:
A Phase III, Multicenter, Randomized, Parallel Group,Double Blind, Double Dummy, Active Controlled Study of Evobrutinib Compared with an Interferon Beta 1a (Avonex®), in Participants with Relapsing Multiple Sclerosis to Evaluate Efficacy and Safety

Summary

EudraCT number	2018-004700-19
Trial protocol	BG
Global end of trial date	20 May 2020

Results information

Result version number	v1
This version publication date	20 June 2021
First version publication date	20 June 2021

Trial information

Trial identification

Sponsor protocol code	MS200527_0074

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04032171
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Healthcare KGaA, Darmstadt Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck Healthcare KGaA, Darmstadt Germany, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the the efficacy and safety of evobrutinib administered orally twice daily versus Interferon-beta-1a (Avonex®), once a week intramuscularly in subjects with Relapsing Multiple Sclerosis (RMS).

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	1
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 950 subjects were planned to be included however, only 1 subject was enrolled in Evobrutinib + Avonex® matched Placebo and no subject was enrolled in Avonex® + Evobrutinib matched Placebo (no results reported in the draft) due to early termination of study.

Pre-assignment

Screening details:

Study was conducted in 2 periods; double blind period and open label extension (OLE) period. However, due to early termination of study, sponsor decided not to conduct the OLE period. Total of 950 subjects were planned to be included in 1:1 to treatment with evobrutinib or Avonex, however only 1 subject was enrolled in evobrutinib.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Arm title	Evobrutinib + Avonex® matched Placebo

Arm description:

Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.

Arm type	Experimental
Investigational medicinal product name	Evobrutinib
Investigational medicinal product code	M2951
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received active evobrutinib BID.

Investigational medicinal product name	Avonex® matched Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subject received IM injection of placebo matched to Avonex® once a week.

Number of subjects in period 1	Evobrutinib + Avonex® matched Placebo
Started	1
Completed	0
Not completed	1
Study Termination	1

Baseline characteristics

Reporting groups	
Reporting group title	Evobrutinib + Avonex® matched Placebo
Reporting group description:	
Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.	

Reporting group values	Evobrutinib + Avonex® matched Placebo	Total	
Number of subjects	1	1	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	1	1	
>=65 years	0	0	
Sex: Female, Male Units: Subjects			
Female	0	0	
Male	1	1	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	1	1	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Evobrutinib + Avonex® matched Placebo

Reporting group description:

Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.

Primary: Annualized Relapse Rate (ARR)

End point title	Annualized Relapse Rate (ARR)[1]

End point description:

The annualized relapse rate at 96 weeks was to be calculated based on qualified relapses. A qualifying relapse is the occurrence of new or worsening neurological symptoms attributable to MS. The relapse should be accompanied by an increase of 0.5 points or more on Expanded Disability Status Scale (EDSS), or 2 points increase on one of the Functional System Scores (FSS), or 1 point increase on at least two of the FSS. The increase in FSS scores must be related to the neurological symptoms which were reported as new or worsening. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Primary

End point timeframe:

At Week 96

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data for efficacy analysis was not collected and evaluated due to early termination of study.

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: per year				
arithmetic mean (standard deviation)	()			

Notes:

[2] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of 12-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point title	Time to First Occurrence of 12-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point description:

EDSS is an ordinal scale in half-point increments that measures disability in participants with MS. EDSS progression is defined as an increase of 1 point or more from Baseline EDSS score when the Baseline score is 5.0 or less, and an increase of 0.5 points or more when the Baseline score is 5.5 or greater. Time to first occurrence of 12-week confirmed EDSS progression is defined as the time from

randomization to the first EDSS progression event that was confirmed at a regularly scheduled visit at least 12 weeks later. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline up to 96 weeks

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: Weeks				
median (confidence interval 95%)	(to)			

Notes:

[3] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Occurrence of 24-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point title	Time to First Occurrence of 24-Week Confirmed Expanded Disability Status Scale (EDSS) Progression

End point description:

EDSS is an ordinal scale in half-point increments that measures disability in participants with MS. EDSS progression is defined as an increase of 1 point or more from Baseline EDSS score when the Baseline score is 5.0 or less, and an increase of 0.5 points or more when the Baseline score is 5.5 or greater. Time to first occurrence of 24-week confirmed EDSS progression is defined as the time from randomization to the first EDSS progression event that was confirmed at a regularly scheduled visit at least 24 weeks later. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline up to 96 weeks

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: Months				
arithmetic mean (standard deviation)	()			

Notes:

[4] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) Short Form Score at Week 96

End point title	Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Physical Function (PF) Short Form Score at Week 96

End point description:

PROMIS Physical function outcome measure assesses various aspects related to a subject's participation in physical activity. The PROMIS measure has 10 items that parents rate on a 5-point likert scale, where 5 indicates "Without any difficulty" and 1 indicates "Unable to do". Responses were summed and converted to standardized T-Scores where higher scores indicates higher PF. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: T-Score				
arithmetic mean (standard deviation)	()			

Notes:

[5] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form Score at Week 96

End point title	Change From Baseline in Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form Score at Week 96

End point description:

The PROMIS Fatigue item bank includes 95 items assessing the experience (frequency, duration, and intensity) as well as the impacts of fatigue on physical, mental and social activities. An 8-item short-form specific to MS was used each measured on a 5-point Likert scale with question (example: How often did you feel tired?) where, 1=never, 2=rarely, 3=sometimes, 4=often, 5=always. Measures from

the fatigue item bank were scored on a T-score metric where, higher scores indicates higher fatigue. Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

Baseline, Week 96

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: T-Score				
arithmetic mean (standard deviation)	()			

Notes:

[6] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Gadolinium-Enhancing (Gd+) Time Constant 1 (T1) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point title	Total Number of Gadolinium-Enhancing (Gd+) Time Constant 1 (T1) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point description:

Total number of Gd+ T1 lesions was to be assessed using magnetic resonance imaging (MRI). Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

At Week 24, 48 and 96

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: Lesions				
arithmetic mean (standard deviation)	()			

Notes:

[7] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of New or Enlarging Time Constant 2 (T2) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point title	Total Number of New or Enlarging Time Constant 2 (T2) Lesions Assessed by Magnetic Resonance Imaging (MRI) Scans at Week 24, 48, and 96

End point description:

Total number of new or enlarging T2 lesions was to be assessed using magnetic resonance imaging (MRI). Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527-0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early, therefore, it was decided as per Statistical Analysis Plan not to report the efficacy data for this study.

End point type	Secondary

End point timeframe:

At Week 24, 48 and 96

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: Lesions				
arithmetic mean (standard deviation)	()			

Notes:

[8] - As per Statistical Analysis Plan, efficacy data were not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events, Serious TEAEs and Adverse Events of Special Interest (AESIs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events, Serious TEAEs and Adverse Events of Special Interest (AESIs)

End point description:

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product. TEAE is an AE that started after study drug treatment; or if the event was continuous from baseline & was serious, related to investigational medicinal product (IMP), or resulted in death, discontinuation, interruption or reduction of study therapy. TEAEs included both serious and non-serious TEAEs. AESIs included liver AEs (possible drug-induced, non-infectious, non-alcoholic and immune-mediated)

infections (serious and opportunistic infections), lipase and amylase elevation, and seizure. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Baseline up to Week 108

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
Subjects With AESIs	0			
Subjects with TEAEs	1			
Subjects with Serious TEAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) Based on Severity According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) Based on Severity According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point description:

Adverse event (AE) was defined as any untoward medical occurrence in a subject, which does not necessarily have causal relationship with treatment. Serious AE was defined as an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in subject hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs included both serious TEAEs and non-serious TEAEs. Severity of TEAEs were graded using NCI CTCAE v4.03 toxicity grades, as follows: Grade 1= Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening and Grade 5 = Death. Number of subject with TEAEs based on severity were reported. Safety analysis set (SAF) included all subjects who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Baseline up to Week 108

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
Grade 1	1			
Grade 2	0			
Grade 3	0			
Grade 4	0			
Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP)

End point title	Vital Signs: Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP)

End point description:

DBP and SBP were measured in semi-supine position after 5 minutes rest for the participants at indicated time points. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Baseline up to Week 108

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Millimeters of mercury (mmHg)				
number (not applicable)				
DBP: Day 1 (n=1, 0)	72			
DBP: Week 2 unscheduled 1 (n=1, 0)	68			
DBP: Week 12 (n=1, 0)	76			
DBP: Week 96/ED (n=1, 0)	84			
SBP: Day 1(n=1, 0)	124			
SBP: Week 2 unscheduled 1 (n=1, 0)	119			
SBP: Week 12 (n=1, 0)	130			
SBP: Week 96/ED (n=1, 0)	140			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Pulse Rate and Respiratory Rate

End point title	Vital Signs: Pulse Rate and Respiratory Rate

End point description:

Pulse rate and Respiration rate was measured in semi-supine position after 5 minutes rest for the participants at indicated time points. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1, Week 2 unscheduled 1, Week 12 and Week 96 ED (Early discontinuation)

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: breaths/minute				
number (not applicable)				
Pulse rate: Day 1 (n=1, 0)	71			
Pulse rate: Week 2 unscheduled 1 (n=1, 0)	77			
Pulse rate: Week 12 (n=1, 0)	75			
Pulse rate: Week 96/ED (n=1, 0)	80			
Respiratory rate: Day 1 (n=1, 0)	12			
Respiratory rate: Week 2 unscheduled 1 (n=1, 0)	18			
Respiratory rate: Week 12 (n=1, 0)	12			
Respiratory rate: Week 96/ED (n=1, 0)	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Temperature

End point title	Vital Signs: Temperature

End point description:

Temperature was measured in semi-supine position after 5 minutes rest for the participants at indicated time points. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1, Week 2 unscheduled 1, Week 12 and Week 96 ED (Early discontinuation)

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Degree Celsius				
number (not applicable)				
Day 1 (n=1, 0)	36.4			
Week 2 unscheduled 1 (n=1, 0)	36.7			
Week 12 (n=1, 0)	36.9			
Week 96/ED (n=1, 0)	36.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Vital Signs: Weight

End point title	Vital Signs: Weight

End point description:

SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1, Week 2 unscheduled 1, Week 12 and Week 96 ED (Early discontinuation).

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: kilogram (kg)				
number (not applicable)				
Day 1 (n=1, 0)	91.4			
Week 2 unscheduled 1 (n=1, 0)	92.3			
Week 12 (n=1, 0)	92.6			
Week 96/ED (n=1, 0)	95.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Abnormal Lab Values

End point title	Number of Subjects with Abnormal Lab Values

End point description:

The laboratory parameters included hematology, coagulation, biochemistry and urinalysis. Clinical meaningful was determined by the investigator. Number of subjects with any clinically meaningful change from baseline in laboratory parameters were reported. SAF included all subjects who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Baseline up to weeks 108

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects with Clinically Significant Electrocardiogram (ECG) Abnormalities

End point description:

ECG parameters included heart rhythm, heart rate, QRS intervals, QT intervals, RR intervals and corrected QT (QTc) intervals. Clinical meaningful was determined by the investigator. Number of subjects with clinically meaningful change from baseline in 12-lead ECG were reported. SAF included all subjects who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

Baseline up to week 108

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) A Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) A Level

End point description:

Absolute concentrations of Immunoglobulin (Ig) A was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: gram per liter (g/L)				
number (not applicable)				
Day 1 (n=1, 0)	0.8			
Day 92 (n=1, 0)	0.92			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) G Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) G Level

End point description:

Absolute concentrations of Immunoglobulin (Ig) E was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: grams per liter (g/L)				
number (not applicable)				
Day 1 (n=1, 0)	5.54			

Day 92 (n=1, 0)	6.11			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) M Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) M Level

End point description:

Absolute concentrations of Immunoglobulin (Ig) M was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: grams per liter (g/L)				
number (not applicable)				
Day 1 (n=1, 0)	0.29			
Day 92 (n=1, 0)	0.25			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Concentrations of Immunoglobulin (Ig) E Level

End point title	Absolute Concentrations of Immunoglobulin (Ig) E Level

End point description:

Absolute concentration of IGE level was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: International units per milliliter				
number (not applicable)				
Day 1 (n=1, 0)	14.1			
Day 92 (n=1, 0)	16.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) A Level

End point title	Change From Baseline in Immunoglobulin (Ig) A Level

End point description:

Change from baseline in immunoglobulin (Ig) A level was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1[9]			
Units: gram per liter (g/L)				
number (not applicable)	1			

Notes:

[9] - 0.12

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) E Level.

End point title	Change From Baseline in Immunoglobulin (Ig) E Level.

End point description:

SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1[10]			
Units: International units per milliliter				
number (not applicable)	1			

Notes:

[10] - 2.6

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) G Level

End point title	Change From Baseline in Immunoglobulin (Ig) G Level

End point description:

Change from baseline in immunoglobulin (Ig) G level was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:

At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1[11]			
Units: grams per liter (g/L)				
number (not applicable)	1			

Notes:

[11] - 0.57

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Immunoglobulin (Ig) M Level

End point title	Change From Baseline in Immunoglobulin (Ig) M Level

End point description:

Change from baseline in immunoglobulin (Ig) M level was reported. SAF analysis set included all participants who were administered any dose of any study intervention.

End point type	Secondary

End point timeframe:
At Day 1 and Day 92

End point values	Evobrutinib + Avonex® matched Placebo			
Subject group type	Reporting group			
Number of subjects analysed	1[12]			
Units: grams per liter (g/L)				
number (not applicable)	1			

Notes:
[12] - -0.04

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to 108 Weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	Evobrutinib + Avonex® matched Placebo
Reporting group description: Subjects received active evobrutinib twice daily (BID) along with concomitant intramuscular (IM) injection of placebo matched to Avonex® once a week. Treatment period was planned to be of 96 weeks.	

Serious adverse events	Evobrutinib + Avonex® matched Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Evobrutinib + Avonex® matched Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Nervous system disorders			
Peripheral edema			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Hepatobiliary disorders			

Hypercholesterolemia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2019	- Restructured text on discontinuation of Study Intervention - Clarified role of Sponsor's Medical Monitor - Clarified statistical approach towards primary and secondary endpoints - Adjusted Exclusion Criteria - Clarified use of concomitant therapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Following analysis of open label extension (OLE) data from RMS phase 2 study (MS200527- 0086), it was determined that a change in active comparator warranted in phase 3 RMS comprised of trial MS200527-0074. Consequently, this trial terminated early.

Notes: